N-Quaternary Compounds

Part VIII. Synthesis and Properties of Dihydrothiazolo[3,2-c]pyrimidinium-8-oxides

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Synthetic pathways to the dihydrothiazolo[3,2-c]pyrimidinium ring system have been worked out. The properties of this new class of compounds have been studied and compared with the properties of the analogous dihydrothiazolo[3,2-a]pyridinium series previously synthesized. The 3-carboxy derivatives are difficult to prepare due to ease of decarboxylation. The 8-oxides are substituted in the 7-position by electrophilic reagents. Bromination of an 8-alkoxide led to oxidative cleavage of the ring and formation of a sulphonic acid. With hydroxyl ions there is a competition between pseudobase formation and cleavage of the 5-membered ring through nucleophilic attack on the activated methylene carbon next to the quaternary nitrogen. UV and NMR data are recorded and compared with the corresponding pyridinium series.

In previous reports1-4 we have discussed syntheses and properties of dihydrothiazolo[3,2-a]pyridinium-8-oxides (I). In this work we have replaced the 6-methylene group in the dihydrothiazolo[3,2-a]pyridinium-8-oxide structure with a nitrogen thus giving rise to the analogous dihydrothiazolo[3,2-c]-pyrimidinium-8-oxide series. Since the pyridinium derivative (I), originally isolated from liver hydrolysates,5 contained a methyl group in the 5-position, work was concentrated on the corresponding 5-methyl derivative (II). The best intermediates for the formation of this ring system would appear to be correctly substituted pyrimid-4-thiones. These were synthesized as shown below.

As it was not obvious how 5-hydroxy-2-methylpyrimid-4-one (IV) best could be converted into the thione (IX) the initial studies were carried out on the corresponding 5-O-protected derivative (III). This was obtained by the condensation between the sodium salt of ethyl α-ethoxy-β-oxyacylate and acetamidine.6 The condensation product was obtained as white plates, m.p. 169—171.5°. Sublimation and recrystallisation from ethanol, however, gave white needles, m.p. 163—164°. When these substances were heated

separately to above their melting points and allowed to cool, the substance with the lower melting point was formed. From a warm saturated alcoholic solution the desired crystal modification could be made to precipitate by seeding with the appropriate crystals. The two substances isolated, had quite different IR-spectra in the solid state. That we were here dealing with crystal modifications was further proved by identity in chromatography and spectroscopic properties in solution.

Treatment of III with phosphorus oxychloride furnished the chloro derivative (VI) which, when heated with potassium hydrogen sulphide in ethanol, gave the thiolactam (VIII). It was found, however, that VIII could also be prepared directly from the lactam (III) in 86% yield by treatment with phosphorus pentasulphide in pyridine. The latter reagent was therefore reacted with 4,5-dihydroxy-2-methylpyrimidine which is formulated in its tautomeric lactam form (IV) to better account for the expected differences in reactivities of the two hydroxyl groups. Thus the carbon of the lactam carbonyl group should suffer attack by phosphorus pentasulphide while the 5-hydroxyl carbon should show no electrophilic character and therefore not react with this reagent. This was true experimentally. Treatment of IV with phosphorus pentasulphide in pyridine yielded the 5-hydroxypyrimid-4-thione (IX) in excellent yield.

The 5-bromo thiolactam (X) was synthesized in order to get some more information on the importance of electron availability on the rate of dihydrothiazolo ring formation as discussed below. Bromination of 2-methylpyrimid-4-one furnished the 5-bromo-lactam (V) which was chlorinated with phosphorus oxychloride and further converted to the pyrimid-4-thione (X) by means of potassium hydrogen sulphide.

The readiness with which the dihydrothiazolo ring is formed in the condensation between the thiolactam (XVIII) and a 1,2-difunctional ethane derivative will depend on the electron density on the sulphur since the reaction will proceed by nucleophilic attack by the sulphur onto the carbon carrying a suitable leaving group. The reaction rate could also be expected to depend on the electron density on the annular nitrogen since a nucleophilic attack by this nitrogen is necessary for the cyclisation of the intermediate.
XIX to occur. However, the rate determining reaction seems to be the substitution by sulphur since the intermediate (XIX) has never been isolated. It obviously suffers nucleophilic attack by the nitrogen as soon as formed under the experimental conditions necessary to effect the first step. This is analogous to what we have previously found in the pyridine series. With the electron donating 5-hydroxy or 5-ethoxy group in the pyrimid-4-thione the condensation was effected in DMF in the presence of sodium carbonate or in alcoholic sodium ethoxide. With the deactivating 5-bromo substituent hardly any condensation took place under the above conditions.

Heating VIII with the sodium salt of 2,3-dibromopropionic acid to form the 2-carboxy derivative (XI) resulted in decarboxylation and formation of XV. This was unexpected since the carboxyl group is less activated in the 2-position than in the 3-position and no such tendency was seen in the pyridine series. The 2-carboxy derivative therefore should be prepared via an ester of the dibromopropionic acid.

The mechanism suggested for the addition of pyrid-2-thiones to α-bromoacrylic acid would also depend on the electron availability on the sulphur atom. Thus pyrimid-4-thiones should react more slowly than the corresponding pyrid-2-thiones due to the electronegativity of the second aromatic nitrogen atom. Experimentally it was found that neither VIII nor IX would add to α-bromoacrylic acid in ethyl acetate or acetonitrile to any extent, solvents

which were useful in the pyridine series. Prolonged heating in methanol gave some product, but aqueous methanol was found to be the best solvent system. Thus XIII was obtained by leaving the reaction at room temperature using large excess \( \alpha \)-bromoacrylic acid. Attempts to increase the rate of the reaction by heating led largely to the decarboxylated product (XVII). The 5-bromo derivative (X) reacted only after standing at room temperature for several weeks and was then decarboxylated. Therefore the addition and condensation have taken place, but XIV is not stable under the experimental conditions necessary. In none of the above reactions was it possible to find any of the intermediate (XXII) due to the readiness of cyclisation as compared to the rate of addition of the thiolactam. The addition can be assumed to proceed by a \textit{trans} mechanism.\(^2\) The bromo adduct will undergo nucleophilic substitution in the conformation shown presumably with inversion of the configuration. However, the problem of the mechanism in the second step is subject to a separate study to be reported on later.

The ready decarboxylation is explained by the stabilisation of the carbanion (XXIV) by the neighbouring quaternary nitrogen atom. Electronegative groups in the aromatic nucleus will decrease the electron density on the bridged nitrogen making the 3-carbon atom more electropositive favouring decarboxylation by the above mechanism and stabilizing further the carbanion (XXIV). Electron donating groups would have the opposite effect. The pyridine derivative corresponding to XIII is not decarboxylated under these conditions.\(^2\)

The electron density on the sulphur atom in pyrimid-4-thiones can be increased by salt formation with a strong base. But then the \( \alpha \)-bromoacrylic acid would have to be esterified to prevent salt formation with increase in

\[ \text{electron density in the acrylate system and therefore decreased reactivity towards nucleophilic attack by the sulphur. This has been verified experimentally. Thus the sodium salt of the thiolactam in methanol reacted readily with the methyl ester of \( \alpha \)-bromoacrylic acid. The ester (XXVI) was unstable, readily hydrolyzing to the acid (XIII).} \]

\( \text{Aryl-alkyl thioethers are normally resistant to treatment with 48 \% hydrogen bromide in acetic acid or water, while ethers are attacked with the formation of the corresponding phenol and alkyl bromide.}^{10} \text{ In agreement} \]

Table 1. NMR spectra in TFA.

![Chemical Structure](image)

<table>
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<tr>
<th>Comp.</th>
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<th>Chemical shift in τ values</th>
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with this we found that the $O$-alkyl group in XV could be removed selectively without destruction of the dihydrothiazole ring. The yield of the hydrolysis product (XVII) using HBr in dilute acetic acid was 86%.

The electron deficient pyrimidinium nucleus should be resistant to electrophilic substitution. Bromination of the $8$-oxide (XVII), however, proceeds readily with bromine in ethanol. This is explained by the strong electron donating properties of the phenolate oxygen and its stabilisation of the transition state (XXVII) during the substitution. As in the pyridine series $^4$ XVII was arylated (XXIX) when treated with the diazonium salt of $p$-nitroaniline. The mechanism of this reaction therefore would be as previously discussed.$^4$

The enhanced electron withdrawing properties of the pyrimidinium ring as compared to the pyridinium ring is further demonstrated in the case of sulphoxide formation. Using performic acid hardly any oxidation of the sulphur in XVII took place under conditions which readily yield the sulphoxide of the corresponding pyridine derivative. Forcing conditions increased the amount of sulphur oxidation, but other reactions became dominant.

When the $8$-oxide is $O$-alkylated as in XV the electrons on the oxygen are no longer available to the same extent for participation in resonance and stabilisation of the transition states in electrophilic substitution. It was therefore not surprising to find that XV was not brominated in the aromatic ring. With bromine in ethanol the dihydrothiazole ring was attacked and the product formed has been identified as a sulphonic acid (XXXI). The NMR spectrum in TFA showed the presence of an aromatic proton at $2.43 \tau$ which is at higher field than in pyrimidinium derivatives (Table 2). The two methylene groups, previously part of the thiazole ring, were found as triplets at 6.20 and 5.13 $\tau$. The molecular ion in the mass spectrum was found at $m/e$ 262 ($C_{9}H_{14}N_{2}O_{3}S$). This indicated a sulphonic acid, support for which could be found in the strong IR absorption centered at 1190 cm$^{-1}$ and a weaker band at 1050 cm$^{-1}$, and acidity in aqueous solution. Its UV absorption bands were found at 300 and 250 mp in 0.1 N HCl. These are different from the $S$-alkylated product (XXXVI) discussed below. That the obtained product was $N$-alkylated was confirmed by the UV spectrum of the $N$-methyl derivative (XXXIV) (Table 3). Both substances had the absorption bands at the same wave lengths.

The opening of the thiazole ring in XV is presumably due to attachment of the bromine to the sulphur (XXXIII), whereby the C-4 carbon in the pyrimidine ring becomes so electrophilic that it is attacked by water present in the alcohol used as solvent.

2- and 4-Hydroxypyrimidines are mainly $N$-alkylated.$^{11}$ Accordingly the $N$-methyl derivative (XXXIV), required for UV comparison with the above sulphonic acid (XXXI), was prepared by treating the potassium salt of III with methyl iodide. That the product was $N$-alkylated was further proved by synthesis of the $O$-methyl derivative (XXXV) by reacting sodium methylate with the 2-chloro compound (VI). This product had a different UV spectrum (Table 3).

When XV was brominated with bromine in acetic acid, the reaction took a different course. NMR now showed that it was the methyl group which was attacked (XXXII), but this reaction was not studied in any detail.
While measuring the UV absorption of XV in aqueous sodium hydroxide it was noticed that the absorption quickly changed with time, and that the change taking place with the molecule was only partially reversible on acidification. The 8-oxide (XVII), however, was stable under these conditions. Preparatively, the behaviour of XV towards alkali was studied by dissolution in aqueous 0.1 N sodium hydroxide. The red solution formed on dissolution, was rapidly decolorized with the appearance of a white solid precipitate. The filtrate which contained the above product besides a second component, was preparatively chromatographed on paper in HOAc:H₂O:BuOH (22:50:100). Elution of the band containing the latter component yielded a substance which has been identified as the 4-hydroxyethylthioether (XXXVI). The methylene protons in the thioether group were found as two triplets at 5.19 and 6.17 τ and the UV spectrum was different from that of the N-alkylated product (XXXI) above (Table 3). The postulated structure was confirmed.
Table 3. UV absorption of

\[
\begin{array}{cccccccc}
\text{Comp.} & \text{Substituents} & \text{0.1 N NaOH aq} & \text{0.1 N HCl aq} \\
& & \lambda & \log \varepsilon & \lambda & \log \varepsilon & \lambda & \log \varepsilon \\
x & y & z & & & & & \\
IV & O & OH & H & 295 & 3.92 & 260 & 3.92 & 255 & 3.36 \\
III & O & OC\text{$_2$H$_5$} & H & 275 & 3.87 & 235 & 3.82 & 255 & 3.93 \\
a & O & \text{H} & & 275 & 3.82 & 235 & 3.75 & 255 & 3.99 \\
XXXI & O & OC\text{$_2$H$_5$} & CH$_3$CH$_2$SO$_2$H & 275 & 3.81 & 240 & 3.77 & 255 & 3.96 \\
XXXIV & O & OC\text{$_2$H$_5$} & CH$_3$ & 275 & 3.74 & 240 & 3.71 & 255 & 3.76 \\
XXXV & OCH$_3$ & OC\text{$_2$H$_5$} & -- & 270 & 3.66 & 230 & 3.85 & 270 & 3.80 & 240 & 3.79 \\
V & O & Br & H & 275 & 3.73 & 235 & 3.85 & 275 & 3.75 & 235 & 3.77 \\
VI & Cl & OC\text{$_2$H$_5$} & -- & 285 & 3.66 & -- & -- & 290 & 3.68 & -- & -- \\
IX & S & OH & H & 340 & 3.78 & 245 & 3.70 & 335 & 3.79 & 245 & 3.29 \\
VIII & S & OC\text{$_2$H$_5$} & H & 320 & 3.26 & 265 & 3.57 & 335 & 4.01 & 245 & 3.29 \\
XXXVI & S(CH$_2$CH$_2$OH) & OC\text{$_2$H$_5$} & -- & 275 & 3.56 & 235 & 3.64 & 315 & 3.83 & 240 & 3.56 \\
\end{array}
\]

\textit{a} Intermediate in the synthesis of 5-hydroxy-2-methylpyrimid-4-one.\textsuperscript{7}  \\
\textit{b} 2H-Pyranyl-2-oxy-.
by alkylation of 5-ethoxy-2-methylpyrimid-4-thione (VIII) with ethylene chlorohydrin.

The white solid has been identified as the pseudobase XXXVIII by means of the following findings. The product was readily soluble in organic solvents and therefore no longer contains a quaternary nitrogen atom. The NMR spectrum in carbon tetrachloride showed the pyrimidine proton as a doublet at $3.08 \tau$ ($J=11.0$ cps) and what appeared to be a broad doublet at $-0.5 \tau$ indicative of a hydroxyl group. The presence of a hydroxyl group was confirmed by IR absorption at 3270 cm$^{-1}$. On the addition of a few drops of deuterium oxide the absorption at $-0.5 \tau$ disappeared and the doublet due to the 7-proton collapsed to a singlet.


Table 4. UV absorption of

<table>
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<tr>
<th>Comp.</th>
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<th>0.1 N HCl aq</th>
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<tr>
<td>Ib</td>
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*a Measured quickly before decomposing.  b Too unstable in alkaline solution.
Both the protons in the methyl group and in the methylene group next to the bridged nitrogen atom had been shifted to higher fields than in XV. In dilute hydrochloric acid the starting material, the quaternary aromatic structure (XV), was rapidly regenerated by protonation of the hydroxyl group and water elimination. Thus, in sodium hydroxide there exists competition between hydroxyl ion attack at the electrophilic 3-carbon with opening of the dihydrothiazolo ring and hydroxyl ion addition to the electron deficient pyrimidinium ring at the 7-position.

The NMR data of the pyrimidines have been collected in Tables 1 and 2. In Table 2 the corresponding data \(^{12}\) for the pyrimidinium derivatives (I) have been included. By comparison of these data it can be seen that the 5-methyl group has undergone a paramagnetic shift of 0.3 units, the 3-proton 0.3—0.4 units, the 2-proton 0.2 units, and the 7-proton about 1.0 unit on the introduction of a second annular nitrogen. However, both the pyrimidinium \(^{12}\) and the pyrimidinium-8-oxides have the same long-wave UV absorption (Table 4).

With the oxygen alkylated (XV), there is a blue shift in alkali since the generation of the oxygenate oxygen is not possible. In acid solution, however, the absorptions are the same. In the pyrimidines (Table 3), the 5-alkoxy-pyrimid-4-ones whether N-alkylated or not, have long-wave UV absorptions at 275 \(\mu\) (NaOH) and 255 \(\mu\) (HCl) and therefore can be distinguished from the 4-methoxy derivative (XXXV) where both these absorptions are at 270 \(\mu\). In the 5-hydroxy derivative (IV) the absorption in NaOH is at a higher wavelength, viz. 295 \(\mu\). The UV shifts in the 4-thione and 4-S-alkyl series follow the oxygen pattern above, but are found at higher wavelengths.

Like the pyridine analogues the pyrimidinium derivatives are blue-fluorescent in UV light. The introduction of a bromine quenches the fluorescence.

**EXPERIMENTAL**

Paper Chromatography or TLC on silica gel in the systems BuOH:EtOH:NH\(_4\)OH (4:1:2:1) and BuOH:HCl:H\(_2\)O (100:22:50) have been used in this work. The NMR spectra were recorded on a Varian A-60A spectrophotometer and the UV spectra on a Perkin-Elmer model 137-UV spectrophotometer.

5-Hydroxy-2-methylpyrimid-4-one (IV). This compound was prepared from 2-methyl-5-tetrahydroxy-2'-pyrrolypyrimid-4-one by sulphuric acid hydrolysis as described by Davold.\(^{7}\)

5-Bromo-2-methylpyrimid-4-one (V). 2-Methylpyrimid-4-one \(^*\) (6.1 g, 0.055 mole) was dissolved in water (110 ml) and bromine (8.8 g, 0.06 mole) added dropwise to the stirred solution at room temperature. The colourless solution was evaporated after 1\(\frac{1}{2}\) h leaving the white solid bromo hydrobromide in quantitative yield (14.0 g). Chromatography showed the product to be homogeneous. The free base was obtained by dissolution in water and neutralizing with sodium bicarbonate. The solid thus precipitated had m.p. 226\(\degree\)C (lit.\(^*\) 231—232\(\degree\)).

5-Bromo-4-chloro-2-methylpyrimidine (VII). Prepared by heating 5-bromo-2-methylpyrimid-4-one hydrobromide in phosphorus oxychloride.\(^*\)

5-Ethoxy-2-methylpyrimid-4-one (III). This compound was prepared essentially as described in the literature \(^*\) by the condensation between the sodium salt of \(\alpha\)-ethoxy-\(\beta\)-oxyacrylate and acetanidine in ethanol. The yield was 67 %; white plates from ethanol, m.p. 169—171\(\degree\) (lit. m.p. 167—167\(\degree\) (CHCl\(_3\))). (Found: C 54.71; H 6.30; O 20.53. Calc. for C\(_5\)H\(_4\)N\(_2\)O\(_3\): C 54.84; H 6.54; O 20.75).

Sublimation in vacuo at elevated temperature yielded a second crystal modification; white needles, m.p. 163—164\(\degree\). That this really was a crystal modification was proved

by both products having the same spectroscopic properties in solution. Both forms when heated to above the melting points and slowly allowed to cool down, gave the lower melting crystal modification. From a warm saturated alcoholic solution, however, any desired modification could be obtained by seeding with the appropriate crystals.

4-Chloro-5-ethoxy-2-methylpyrimidine (VI). A solution of 5-ethoxy-4-hydroxy-2-methylpyrimidine (6.34 g, 0.04 mole) in phosphorus oxychloride (40 ml) was refluxed for 3 h, the solution evaporated, the dark coloured gummin residue treated with ice-cold sodium bicarbonate solution until neutralized and the suspension extracted with ether (8 x 30 ml). The extracts were dried, evaporated and the residue distilled to yield a colourless liquid, b.p. 108 - 109°/9 mm Hg which on cooling gave a white solid (4.85 g, 69 %), m.p. 48.5 - 47.5°. This material readily sublimed at 30°/0.005 mm Hg. (Found: C 48.75; H 5.23; Cl 20.35; N 16.49. Calc. for C\textsubscript{7}H\textsubscript{6}ClN\textsubscript{2}O: C 48.71; H 5.26; Cl 20.50; N 16.23).

5-Ethoxy-2-methylpyrimid-4-thione (VIII). a) To a refluxing solution of 4-chloro-5-ethoxy-2-methylpyrimidine (6.04 g, 0.035 mole) in absolute ethanol (80 ml) was added potassium hydrogen sulphide (8.56 g, 0.11 mole) in small portions over 13 h. The reaction was refluxed for another 10 h, evaporated, the residue suspended in water (200 ml), the pH adjusted to 5 with acetic acid and the suspension extracted repeatedly with ether. Evaporation of the dried ether extracts left a yellow solid (1.8 g, 30 %) which crystallized from ethanol in yellow needles, m.p. 177 - 181°. (Found: C 49.50; H 5.78; N 16.68; S 18.82. Calc. for C\textsubscript{7}H\textsubscript{6}N\textsubscript{2}O\textsubscript{2}: C 49.39; H 5.92; N 16.45; S 18.84).

b) 5-Ethoxy-2-methylpyrimid-4-one (15.4 g, 0.1 mole) and phosphorus pentasulphide (21.0 g, 0.11 mole) were stirred together in dry pyridine (340 ml) and the resultant solution refluxed for 80 min. The cold dark reddish solution was poured into water (500 ml) and the resultant solution (pH = 6) evaporated to about 100 ml and left in the cold. A yellowish brown solid (7.7 g) crystallized out. Chloroform extraction of the filtrate (10 x 25 ml) yielded another 7 g of the same solid (in all 14.7 g, 87 %) which was chromatographically homogeneous and identical with the substance prepared above; yellowish-green needles (Et\textsubscript{2}O), m.p. 178 - 181°.

5-Hydroxy-2-methylpyrimid-4-thione (IX). A stirred mixture of 5-hydroxy-2-methylpyrimid-4-one (5.0 g, 0.04 mole) and phosphorus pentasulphide (8.60 g, 0.045 mole) in dry pyridine (130 ml) were refluxed for 31 h, more phosphorus pentasulphide (0.9 g, 0.005 mole) added and the mixture refluxed for another 4½ h. The resultant dark red solution was allowed to cool, poured into water (200 ml) and the solution concentrated to about 80 ml. The reddish crystalline thione was slowly precipitated on standing; yield (4.9 g, 86 %). The analytical sample was recrystallized from benzene-ethanol, m.p. 226 - 228°. (Found: C 41.69; H 4.09; N 19.49; S 23.05. Calc. for C\textsubscript{7}H\textsubscript{6}N\textsubscript{2}O\textsubscript{2}: C 42.13; H 4.21; N 19.73; S 22.53).

5-Bromo-2-methylpyrimid-4-thione (X). To 5-bromo-4-chloro-2-methylpyrimidine (5.8 g, 0.028 mole) in abs. ethanol (80 ml) was added potassium hydrogen sulphide (2.12 g, 0.029 mole) and the reaction mixture heated under reflux for 9 h. The alcohol was evaporated and the residue triturated with water, the yellow solid filtered off, washed well with water and dried, yield 4.85 g (84 %) of a chromatographically homogeneous solid. Further purification could be effected by sublimation at 115°/0.01 mm Hg or recrystallisation from methanol, m.p. 200 - 204°. (Found: C 29.32; H 2.64. Calc. for C\textsubscript{7}H\textsubscript{6}BrN\textsubscript{2}S: C 29.27; H 2.44).

8-Ethoxy-5-methyl-4-1,3-dihydrothiazolo[3,2-c]pyrimidinium bromide (XV). a) To 5-ethoxy-2-methylpyrimid-4-thione (1.70 g, 0.01 mole) dissolved in dry DMF (80 ml) was added anhydrous sodium carbonate (0.53 g, 0.005 mole) and 1,2-dibromoethane (1.88 g, 0.01 mole) dissolved in DMF (20 ml). The addition was carried out dropwise every 5 min. The stirred mixture heated to 70° and kept at this temperature for 3½ h. The reaction mixture was concentrated at reduced pressure to about 20 ml, allowed to cool, the solid precipitate collected and triturated with a little water. There remained a yellowish solid (1.60 g, 58 %); yellow needles from DMF, m.p. 228 - 230°. (Found: C 39.72; H 5.12; N 9.90; S 11.89. Calc. for C\textsubscript{12}H\textsubscript{17}BrN\textsubscript{2}O\textsubscript{5}: C 39.35; H 4.70; N 10.11; S 11.55). The molecular ion in the mass spectrum was found at m/e 197.

b) The reaction was also done in methanolic sodium methoxide by heating under reflux for 6 h. The yield was 68 %.

5-Methyl-1,3-dihydrothiazolo[3,2-c]pyrimidinium-8-oxide (XVII). a) 1,2-Dibromoethane (9.4 g, 0.05 mole) dissolved in DMF (50 ml) was added dropwise with stirring over 30 min

to cold DMF (200 ml) containing 5-hydroxy-2-methylpyrimid-4-thione (7.1 g, 0.05 mole) and sodium carbonate (5.3 g, 0.05 mole). The reaction mixture was heated at 55° for 3 h, evaporated, the residue extracted with ethanol, the residue dissolved in the minimum amount of hot water and the pH adjusted to 3.5–4.0. The white solid precipitate (10.6 g) was a mixture of the zwitterion and the hydrobromide. This material was therefore dissolved in water and passed through a DEAE-Sephadex A-25 column in the formate form. Elution with 0.01 N formic acid furnished the title compound, m.p. 187–189° after recrystallisation from ethanol. (Found: C 49.75; H 4.90; N 16.65. Calc. for C₉H₆N₂O₃: C 50.60; H 4.76; N 16.67). The molecular ion in the mass spectrum was found at m/e 168.

b) 8-Ethoxy-5-methylidihydrothiazolo[3,2-c]-pyrimidinum bromide (0.28 g, 0.001 mole) was dissolved in acetic acid (15 ml) and 48 %aq hydrogen bromide (10 ml) added. The resultant solution was refluxed for 30 h. The yellow solution evaporated and the residue triturated with boiling acetone. The insoluble hydrobromide (0.22 g, 86 %) m.p. 250° was chromatographically and spectrosocopically found to be the same as the material synthesized above.

Attempted preparation of 8-ethoxy-5-methylidihydrothiazolo[3,2-c]pyrimidine-2-carboxylate (XIX). Formation of 8-ethoxy-5-methylidihydrothiazolo[3,2-c]pyrimidinum bromide (XV). To 5-ethoxy-2-methylpyrimid-4-thione (0.51 g, 0.003 mole) dissolved in methanol (25 ml) was added 2.7 N methanolic sodium methoxide solution (1.1 ml, 0.003 mole) and 2,3-dibromopropionic acid (0.70 g, 0.003 mole). The reaction mixture was refluxed for 16 h, the solution evaporated, the residue extracted with boiling acetone to remove any unreacted thioclamid and the organic residue extracted into ethanol. The yellowish-white solid (0.80 g, 69 %) which crystallized from the ethanolic solution on cooling was identified as 8-ethoxy-5-methylidihydrothiazolo[3,2-c]pyrimidinum bromide.

8-Hydroxy-5-methylidihydrothiazolo[3,2-c]pyrimidinum-3-carboxylate (XIII). 5-Hydroxy-2-methylpyrimid-4-thione (0.71 g, 0.005 mole) was dissolved in 50%, aqueous methanol (50 ml). α-Bromoacrylic acid (0.11 g, 0.005 mole) was then added with stirring at room temperature. More α-bromoacrylic acid (4 x 1.0 g) was added over a period of 7 days. The reaction mixture was then evaporated to dryness at reduced pressure with solid residue triturated with ethyl acetate. The hydrobromide (1.0 g, 70 %) thus obtained was chromatographically homogeneous. The zwitterion was liberated on a DEAE-Sephadex A-25 column in the formate form. Elution with 0.01 N formic acid furnished the title compound. Recrystallisation from water gave pale yellow crystalline material, m.p. 171–172°. (Found: C 34.98; H 4.06; N 13.34; S 15.06. Calc. for C₉H₆N₂O₃S: C 34.77; H 3.78; N 13.21; S 15.08). The apparent molecular ion in the mass spectrum was found at m/e 168 (M–44).

3-Carboxethoxy-5-methylidihydrothiazolo[3,2-c]pyrimidinum-8-oxide (XXVI). 5-Hydroxy-2-methylpyrimid-4-thione (0.28 g, 0.002 mole) was dissolved in methanolic (15 ml) sodium methoxide (from 0.046 g of Na, 0.002 mole). A solution of methyl α-bromoacrylate (0.40 g, 0.0025 mole) in methanol (5 ml) was added dropwise over 5 min to the stirred solution. The stirred solution was left for 2 h at room temperature, kept at 60° for 2 h, left in the cold, the precipitated inorganic salt filtered off, the filtrate evaporated and the residue triturated with ether and then acetone. There remani a yellow crystalline solid (0.25 g, 54 %) slightly contaminated with inorganic material, but chromatographically homogeneous. Attempts to prepare an analytical sample were unsuccessful due to the ease with which the ester was hydrolysed to the acid (XIII). The molecular ion in the mass spectrum was found at m/e 226 (C₉H₆N₂O₃S).

8-Ethoxy-5-methylidihydrothiazolo[3,2-c]pyrimidinum-3-carboxylate (XII). α-Bromoacrylic acid (0.45 g, 0.003 mole) in methanol (10 ml) was added dropwise with stirring to a solution of 5-ethoxy-2-methylpyrimid-4-thione (0.54 g, 0.002 mole) in methanol (15 ml) at room temperature. After standing for 2 days more α-bromoacrylic acid (0.15 g, 0.001 mole) was added to the solution which was then kept at 60° for 10 h. The solution was then evaporated at reduced pressure and unreacted thioclamid extracted into ethyl acetate. Chromatography showed the residual pale yellow solid to be essentially homogeneous (0.48 g, 75 %). This material was used as such in spectroscopic measurements, but attempts to prepare an analytical sample of the above hydrobromide or the zwitterion invariably lead to some decarboxylation.

8-Bromo-5-methylidihydrothiazolo[3,2-c]pyrimidinum bromide (XVIII). A solution of 5-bromo-2-methylpyrimid-4-thione (0.10 g, 0.0005 mole) and α-bromoacrylic acid (0.15 g,

0.001 mole) in ethyl acetate (5 ml) was left at room temperature for several weeks. The solid precipitate (0.09 g, 56%) was then filtered off and washed with ether and ethanol to remove any coprecipitated thiocarbamid. Attempts to prepare an analytical sample were dropped due to the ease with which the substance decomposed. The structure was confirmed by NMR and by mass spectrum, the molecular ion being at m/e 231 (233) (C₆H₅BrN₃S).

The above compound was also formed in the condensation between the above thiocarbamid and 2,3-dibromothiolethane in DMF with sodium carbonate at 46°C.

7-Bromo-8-hydroxy-5-methylthiohydrothiazolo[3,2-c]pyrimidinum bromide (XXXVIII). 5-Methylthiohydrothiazolo[3,2-c]pyrimidinum-8-oxide (1.68 g, 0.01 mole) was dissolved in 96% ethanol (200 ml) and bromine (3 ml, 0.01 mole) added. The solution was refluxed for 3 h. The pale yellow bromo hydrobromide crystallized out on cooling (1.50 g, 46%, m.p. 260°C (decomp.)). The analytical sample was recrystallized from ethanol. (Found: C 26.38; H 2.54; Br 47.16; N 8.38. Calc. for C₇H₅BrN₃O₂S: C 25.61; H 2.44; Br 48.84; N 8.58) This analysis indicates the presence of a little free witterion confirmed by alkali titration of the HBr.

5-Methyl-7-p-nitrophenylthiohydrothiazolo[3,2-c]pyrimidinum-8-oxide (XXIX). p-Nitroanilin (0.56 g, 0.005 mole) in 2 N HCl (15 ml) was diazotized by addition of sodium nitrite (0.35 g, 0.005 mole) in water (20 ml) at 0–5°C. A solution of 5-methylthiohydrothiazolo[3,2-c]pyrimidinum-8-oxide (0.84 g, 0.005 mole) in saturated sodium bicarbonate solution (20 ml) was added dropwise over 5 min to the diazonium solution at 0–5°C. The pH of the reaction mixture was brought to 7.5 with more of the sodium bicarbonate solution and the red solid collected by filtration, yield 0.93 g (59%), m.p. > 275°C. (Found: C 53.50; H 3.54; N 14.85. Calc. for C₆H₅N₃O₂S: C 53.85; H 3.80; N 14.54). The molecular ion in the mass spectrum was at m/e 290.

Bromination of 8-ethoxy-5-methylthiohydrothiazolo[3,2-c]pyrimidinum bromide (XV). 8-Ethoxy-5-methylthiohydrothiazolo[3,2-c]pyrimidinum bromide (1.07 g, 0.04 mole) was dissolved in 96% ethanol (100 ml) and excess bromine (7 ml) added. The solution was refluxed for 7 h. Chromatography then showed that all the starting material had reacted. The product consisted largely of one component. The solution was evaporated and the residue triturated with alcohol. There remained a solid (0.4 g, 40%), m.p. 199–200°C which has been identified as 5-ethoxy-2-methyl-1-(2-sulphonylthio) pyrimid-4-one (XXX). Recrystallisation from ethanol gave white needles, m.p. 193–194°C. (Found: N 10.41; S 12.09. Calc. for C₅H₅N₃O₂S: N 10.69; S 12.18).

2,3-Dimethyl-5-ethoxy-4-one (XXXIV). 5-Ethoxy-2-methylpyrimid-4-one (2.31 g, 0.015 mole) was dissolved in ethanolic (20 ml) potassium hydroxide (0.84 g, 0.015 mole) and methyl iodide (15 ml) added. The resultant solution was refluxed for 1 h, the precipitated inorganic salt filtered off from the cold reaction mixture, the filtrate evaporated and the residual material triturated with acetone. A white solid remained (1.8 g). Chromatography showed this to contain a second component presumably the quaternary O- and N-alkylated material. Part of this material was therefore sublimed at 110°C/0.05 mm Hg, snow-white crystals, m.p. 103°C. (Found: N 18.80. Calc. for C₉H₁₁N₃O₄: N 16.67). The molecular ion in the mass spectrum was found at m/e 168 (C₉H₁₂N₃O₄).

5-Ethoxy-4-methoxy-2-methylpyrimidine (XXXV). Sodium (0.14 g, 0.006 mole) was reacted with methanol (50 ml) and 4-chloro-5-ethoxy-2-methylpyrimidine (0.86 g, 0.005 mole). The reaction mixture was heated under reflux for 2 h, allowed to cool, the filtrate evaporated, the residue dissolved in water (20 ml) the pH adjusted to 7 with sodium bicarbonate, the solution extracted with ether and the ether extracts dried, evaporated, and the residue distilled; colourless liquid, b.p. 110°C/14 mm Hg, yield 0.50 g (60%). (Found: N 16.42. Calc. for C₉H₁₅N₃O₄: N 16.67). The molecular ion in the mass spectrum was found at m/e 168.

Behaviour of 5-ethoxy-2-methylthiohydrothiazolo[3,2-c]pyrimidinum bromide (XV) in 0.1 N NaOH aq. 8-Ethoxy-5-methylthiohydrothiazolo[3,2-c]pyrimidinum bromide (0.54 g, 0.002 mole) was added to 0.1 N NaOH aq (20 ml). The resultant red solution was rapidly decolorized with the precipitate of a white solid (0.10 g, 24%). Chromatography of the filtrate showed this to contain more of the above precipitate besides a second major component. The filtrate was therefore neutralized, concentrated to a small volume and subjected to preparative paper chromatography using HOAc:CH₃OH:BuOH (22:50:100). Elution of the band with Rf ≈ 0.9 yielded a substance which was identified as 5-ethoxy-4-(2-hydroxyethio)-2-methylpyrimidine (XXXVI). This was confirmed by synthesis.

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The first precipitated solid gave snow-white crystals on sublimation at 160°/0.01 mm Hg, m.p. 84—85°. (Found: C 50.66; H 6.57; N 13.25; S 14.69. Calc. for C₅H₅N₃O₃S: C 50.47; H 6.54; N 13.08; S 14.95). UV $\lambda_{\text{max}}$ in 0.1 N NaOH aq: 290 mµ (3.98). NMR (CDCl₃): 8.63 and 6.18 (triplet and quartet, $J=7.0$ cps, OEt), 6.85 and 5.58 (triplets, $J=8.6$ cps, -8-CH$_2$-CH$_2$-N respectively), 3.08 (doublet, $J=10.8$ cps, 7 H) and a partially collapsed doublet at $-0.5 \tau$ (7.0 H). On addition of a few drops of deuterium oxide the absorption at $-0.5 \tau$ disappeared and the doublet due to the 7-proton (3.08) collapsed to a singlet.

Dissolution in 2 N HCl and re-evaporation furnished the starting material viz. 8-ethoxy-5-methylthiodydrothiazolo[3,2-c]pyrimidinium bromide (XV).

High resolution mass spectrometry gave molecular ion $m/e$ 214.0773 (C₅H₅N₃O₃S). The substance, from the above evidence, must be 8-ethoxy-7-hydroxy-5-methylthiodydrothiazolo[3,2-c]1,4-diarylpyrimidine (XXXVIII),

5-Ethoxy-4-(2-hydroxyethyl)-2-methylpyrimidine (XXXVI). 5-Ethoxy-2-methylpyrimid-4-thione (0.85 g, 0.005 mole) in water (10 ml) was dissolved by addition of 2 N NaOH aq. (3.8 ml, 0.0076 mole). Ethylene chlorhydrin (0.61 g, 0.0076 mole) was added dropwise to the stirred solution. The reaction mixture was stirred at room temperature for 24 h, pH adjusted to 7 with HCl, and the mixture extracted with ether. The dried ether extract was evaporated and the residual solid (0.6 g, 50 %) sublimed at 55°/0.01 mm Hg, white solid, m.p. 64—66°. (Found: C 50.37; H 6.50; N 12.91. Calc. for C₅H₅N₃O₃S: C 50.47; H 6.54; N 13.08).

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